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VASCULITIS (LUIS R. ESPINOZA, SECTION EDITOR)

Churg-Strauss Syndrome: An Update

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Abstract Churg-Strauss syndrome is an uncommon disease of unknown cause described initially by Churg and Strauss in 1951. Even though it was initially thought to be a variant of polyarteritis nodosa, its pathological, clinical, and laboratory features show that it is related to the small vessel vasculitides, and it is now classified as an antineutrophil cytoplasmic antibody–associated vasculitis. The presence of asthma, usually of adult onset, along with other allergic symptoms, peripheral and tissue eosinophilia, is specific to this disease. These features usually help clinicians distinguish it from other types of small vessel vasculitis and should alert clinicians about its presence. Two different clinical subtypes defined by the presence of antineutrophil cytoplasmic antibodies recently have been recognized. Recent advances in the treatment and pathophysiology of Churg-Strauss syndrome are reviewed in this article.

Keywords Churg-Strauss syndrome (CSS) · Vasculitis · Eosinophils · ANCA-associated vasculitis

Introduction

Churg-Strauss syndrome (CSS) is an uncommon systemic necrotizing vasculitis that involves small and middle-sized blood vessels of different organs, such as the lungs, peripheral nerves, skin, heart, and gastrointestinal tract. One of the main characteristics of this syndrome is its association with allergic syndromes such as asthma, sinusitis, and rhinitis. It shares certain clinical and pathologic features with granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis [1], and polyarteritis nodosa [2, 3]. The original description of a distinct clinical syndrome was reported by Churg and Strauss [3] in 1951, followed by a large 111-case series by Rose and Spencer [4]. In both series, patients had a significantly higher frequency of blood eosinophilia, tissue eosinophilia, and extravascular necrotizing and granulomatous lesions, which was in contrast to patients with classic and polyarteritis nodosa. The characteristics of the asthma associated with these cases were distinct from those of common allergic asthma. Differences included a late onset, lack of family history of allergies, association with very specific parenchymal lung lesions, and a degree of eosinophilia higher than expected in allergy-induced asthma [3, 4]. CSS has been classified as an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, along with granulomatosis with polyangiitis and microscopic polyangiitis (MPA), although these antibodies are present in only 40% of cases [5•].

Epidemiology

CSS usually manifests between 7 and 74 years of age, with a mean age at onset of 38 to 54 years [5•, 6, 7]. A recent review of CSS in the pediatric population identified reports in children as young as 4 years of age [8]. The estimated incidence is approximately 0.11 to 2.66 new cases per 1 million population per year, with an overall prevalence of 10.7 to 14 per 1 million adults [5•, 9]. There is no significant gender difference, although some studies have

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shown a slight male predominance. CSS is less common than GPA, with a similar incidence rate to that of MPA [8].

Etiopathogenesis

Although it is still an idiopathic condition, recent significant advances have been made to aid in the understanding of the pathogenic processes in CSS. Eosinophil infiltration and ANCA-induced endothelial damage are probably the most important mechanisms of disease in this condition.

Eosinophils

Some studies suggest a direct pathogenic effect of tissue eosinophilic infiltration in CSS [10•]. Eosinophils traditionally have been considered to be end-stage effector cells acting through the release of chemotactic lipid mediators and cationic proteins from eosinophilic granules [11]. These proteins include eosinophil peroxidases, lysophospholipases, eosinophil-derived neurotoxin, eosinophil granule major basic protein, and eosinophilic cationic protein and are believed to induce direct tissue damage [8, 12].

Eosinophils have the potential to secrete cytokines, including interleukin (IL)-1, IL-3, vascular endothelial cell growth factor, transforming growth factor (TGF)-α and TGF-β, and IL-5. It is believed that via the production of TGF and by stimulating TGF release from platelets, these cells stimulate fibroblast proliferation and collagen deposition, which may be an important defense against large organisms such as parasites but may also cause tissue fibrosis [13].

IL-5 was initially found to be secreted by T cells to induce differentiation of B lymphocytes into antibody-forming cells. However, recently it has been found to play a pivotal role in the maturation, differentiation, and survival of eosinophils through multiple roles, such as inducing development and proliferation in the bone marrow, delaying apoptotic death, inducing eosinophil chemotaxis, increasing adhesion to endothelial cells, and enhancing effector functions [10•, 12].

It has been increasingly recognized that eosinophils play an important role as antigen-presenting cells. They express major histocompatibility complex class II molecules and co-stimulatory molecules such as CD-40 that are required for the presentation of antigens from the extracellular environment. Recent important evidence suggests that eosinophils have the ability to stimulate naïve and previously primed T cells [11].

Despite the presence of eosinophils in tissues and peripheral blood in patients with CSS, evidence of direct damage to the tissues in CSS is lacking [10•]. Eosinophils may play another important role in the pathogenesis of CSS by inducing T-helper type 2 (Th2) responses through activation of T cells [14, 15]. Activated T cells have been found in vasculitic lesions, and markers of T-cell activation have been found in these patients [10•, 15].

Recent studies have implicated IL-25, a cytokine produced by eosinophils, basophils, mast cells, and endothelial cells, in the pathogenesis of CSS via the enhancement of Th2 cytokine production. In this study, higher levels of IL-25 were found in serum of patients with active CSS compared with patients with hypereosinophilic syndrome (HES), atopy, and healthy controls. They also correlated with eosinophil counts 10 times higher than those found in control patients with HES and atopy [16•]. Levels of other cytokines responsible for the recruitment of Th2 cells, such as CCL17/thymus and activation-regulated chemokine, have been found in the serum and Th2 cells infiltrating the tissues of patients with CSS and HES. These levels correlated with disease activity, elevated eosinophil counts, and IgE levels [17].

Antineutrophil Cytoplasmic Antibodies

The presence of ANCA and its correlation with clinical activity has been observed in in vitro and clinical studies [18], and its role in the pathogenesis of small vessel vasculitic syndromes was demonstrated by elegant experiments in animal models [19]. ANCAs are believed to activate neutrophils that cause direct damage to endothelial cells by releasing lytic enzymes and oxygen radicals, and by activating complement [18].

ANCA levels are seen in approximately 40% of CSS cases, usually a perinuclear pattern associated with elevated anti-myeloperoxidase antibodies [7, 20, 21]. The presence of ANCA seems to correlate with an increased incidence of renal involvement, peripheral neuropathy, and biopsy-proven vasculitis, with a lower incidence of cardiac and lung disease in patients with CSS [20]. Other manifestations that have been found to be more common in ANCA-positive patients include alveolar hemorrhage, purpura, mononeuritis multiplex, and central nervous system involvement [21, 22].

Based on some studies, it is now believed that ANCA may cause damage to the vascular endothelium in ANCA-positive CSS patients in the same way that it may cause damage in granulomatosis with polyangiitis and microscopic polyangiitis, whereas ANCA-negative patients may have tissue damage secondary to the release of inflammatory mediators and cationic proteins from eosinophils [5•, 23].

Environmental Factors

Different environmental factors have been found to potentially trigger CSS, including allergens, infections, vaccinations, and

medications [24]. Among medications, special attention has been placed on the leukotriene receptor antagonists traditionally used to treat asthma. It is now believed that these agents better control the asthmatic component in patients with CSS, allowing for a decrease or discontinuation of the glucocorticoids, which may be controlling the vasculitic component, and thus, it becomes clinically evident [25]. A similar phenomenon has been reported recently in patients with asthma treated with the IgE antagonist omalizumab, which may unmask CSS once the steroids are discontinued [26].

Genetics

The genetic factors involved in the development of CSS have not been studied as extensively as in GPA. The difficulties in performing genetic association studies in ANCA-associated vasculitis include small sample sizes and discrepancies regarding whether to classify these conditions based on ANCA status or based on clinical features [27, 28]. *HLA-DRB1* alleles and *HLA-DRB3* and *HLA-DR4* genes have been associated with CSS in two studies from Italy and Germany [29, 30]. One of these studies also found that the presence of *HLA-DRB4* in CSS correlated with the presence of vasculitic symptoms characteristic of the ANCA-positive subset, such as mononeuritis multiplex, palpable purpura, and alveolar hemorrhage [29].

Clinical Manifestations

Three phases, which frequently overlap, have been described in CSS. An initial prodromal phase is common; lasts months to years; and may include arthralgias, myalgias, malaise, fever, and weight loss [5•, 8, 31, 32]. Asthma is the main manifestation during the prodromal phase, as it is present in 96% to 100% of patients. In patients with CSS, the asthma is usually of adult onset and tends to be severe and more refractory to treatment [5•, 32]. Asthma precedes the onset of vasculitis by an average of 3 to 9 years, although it has been reported after up to 30 years, perhaps delayed by corticosteroid treatment, which may partially control and delay the onset of vasculitic symptoms [3, 5•, 8, 31]. The asthma often starts to improve, becomes easier to treat, and may even enter remission right before the onset of vasculitis, as described in the initial report by Churg and Strauss [3].

In this initial phase, upper respiratory symptoms are present in the majority of patients (47%–93%) [5•, 33]. They include nasal polyps, allergic rhinitis, and recurrent or chronic sinusitis. Lesions seen in granulomatosis with polyangiitis, such as nasal or sinus granulomas, hemorrhage, and crusting, are quite uncommon; however, orbital involvement has been reported [5•, 33].

The second phase presents with peripheral eosinophilia and may be associated with organ involvement. Characteristic eosinophilic infiltrates occur in the lungs or the gastrointestinal tract, causing an eosinophilic gastroenteritis [5•, 32, 34]. The pulmonary infiltrates are present in up to half of the patients during this phase. They are more frequently peripheral and can be patchy, asymmetrical, and occasionally nodular (which rarely cavitate). Pleural and pericardial effusions can be present [5•, 32, 34, 35]. The symptoms of eosinophilic gastroenteritis include abdominal pain, nausea, vomiting, diarrhea, and occasionally gastrointestinal bleeding. It is associated with peripheral eosinophilia and usually precedes the vasculitis [8].

In the second phase, the eosinophil count is usually higher than 10% of the differential leukocyte count, or greater than 1,500/mm^3 [5•, 31, 36]. The third phase of the disease has been associated with the onset of vasculitis. Involvement of the peripheral nervous system is the most important manifestation of vasculitis in CSS. Patients may present with mononeuritis multiplex or a mixed sensorimotor peripheral neuropathy. The presence of drop wrist or foot is the typical manifestation of mononeuritis multiplex, and this may be confirmed by nerve conduction studies or sural nerve biopsy, which typically shows inflammation of the vasa nervorum [2, 3, 31, 32]. Central nervous system involvement accounts for 25% of cases with neurological involvement. Patients may present with cerebral infarctions and hemorrhage. Although central nervous system involvement is uncommon, some series have it as the second cause of mortality in CSS [31, 32, 37].

Cutaneous lesions of CSS have been classified into three categories: extravascular granulomas, leukocytoclastic vasculitis, and cutaneous polyarteritis nodosa. More than one type of lesion can be seen in the same patient [38]. Palpable purpura, subcutaneous nodules, and livedo reticularis are the most common skin manifestations and may be present in up to 68% of cases [39]. Extravascular cutaneous granulomas have been called *Churg-Strauss granuloma*. The occurrence of this lesion was initially thought to be pathognomonic of CSS, but it can be seen in other vasculitides, autoimmune disorders, hematologic and infectious processes, and in patients without a recognized underlying disease [40]. Skin biopsies are easy to perform and frequently valuable in the confirmation of the diagnosis [5•].

Cardiac involvement is very common in patients with CSS and is the leading cause of mortality [3, 41•, 42]. According to one study, cardiac involvement may be present in 62% of the cases; however, many of these cases are asymptomatic, as only 26% of cases may present with clinical symptoms [41•]. The same study revealed electrocardiographic abnormalities in 66% of the

cases, abnormal echocardiography findings in 50%, and MRI detected problems in 62% of patients [41•]. Manifestations may vary and include myocarditis, congestive heart failure, eosinophilic pericardial effusions, tamponade, valvular disease, and (less commonly) coronary vasculitis. The presence of cardiac involvement heralds a poor prognosis and higher mortality, and early detection of heart involvement is of utmost importance [3, 41•, 42]. Recent studies have shown that the absence of ANCA and the presence of high eosinophil counts correlate best with cardiac involvement, of which endomyocarditis is associated with worse prognosis and increased mortality [42]. As in other organ involvement, gastrointestinal manifestations are mainly related to two mechanisms: eosinophilic infiltration of the bowel wall or vasculitis.

Depending on the area of involvement, different clinical manifestations may be seen. Submucosal involvement may cause masses and obstruction, mucosal involvement may cause diarrhea and bleeding, peritonitis may lead to eosinophil-rich ascitis and abdominal pain, and mesenteric vasculitis may lead to bowel ischemia [43]. Rare cases of intestinal perforations, gallbladder involvement, and pancreatitis have been reported [5•, 43, 44].

Renal involvement is less common than in MPA and GPA, but it is seen in approximately 25% of the patients with CSS. The main manifestation is a necrotizing crescentic glomerulonephritis associated with the presence of ANCA. Less common manifestations include eosinophilic interstitial nephritis, mesangial glomerulonephritis, and focal sclerosis [45].

Diagnosis

A group of vasculitis experts from the American College of Rheumatology met in 1990 and developed a set of six diagnostic criteria for CSS: asthma, eosinophilia greater than 10% on a differential white blood cell count, mononeuropathy (including mononeuritis multiplex) or polyneuropathy, nonfixed pulmonary infiltrates on chest x-rays, paranasal sinus abnormality, and the presence of extravascular eosinophils on a biopsy containing a blood vessel. The presence of four or more of these six criteria yielded a sensitivity of 85% and a specificity of 99.7% [36].

Besides a high eosinophilic count and a positive ANCA on blood work, the rest of the blood tests do not help much in the diagnosis of this condition. The presence of small vessel vasculitis on tissue biopsy and the presence of any of the above clinical criteria should alert the clinician about the diagnosis.

Several conditions may be confused with CSS and should be included in the differential diagnosis. Patients with HES may also present with history of allergy, skin involvement, pulmonary infiltrates, eosinophilia, and myocardial involvement [46]. In contrast, HES is usually refractory to steroid therapy, systemic vasculitis and granulomas are absent on biopsy, and certain typical findings of HES (eg, endomyocardial fibrosis) are rare in CSS. Chronic eosinophilic pneumonia may be confused with the pulmonary involvement of CSS, but it is limited to the lungs and not associated with vasculitis or granulomas [46]. Other systemic vasculitides may involve the same organs as CSS and may also be ANCA positive, but the presence of asthma and eosinophilia is uncommon [8, 36]. Hypersensitivity vasculitis, eosinophilic granulomas, sarcoidosis, cutaneous eosinophilic vasculitis, infectious granulomatous processes, and drug reactions may share some pathological features, but details of the clinical picture should help distinguish these entities from CSS [8, 36].

Two Different Conditions?

Even though CSS has been considered a distinct entity, recent observations have pointed out two different disease patterns based on the clinical and laboratory features and the presence or absence of ANCA [20, 21]. ANCA-positive patients tend to have a higher incidence of necrotizing glomerulonephritis, purpura, alveolar hemorrhage, neuropathy, and biopsy-proven vasculitis. ANCA-negative patients have had higher eosinophilic counts and tissue infiltration, parenchymal lung disease, heart disease, and fever [5•, 23].

These findings led to the hypothesis that ANCA causes endothelial damage leading to a vasculitic picture, whereas eosinophilic infiltration leads to direct tissue damage induced by production of cardiotoxic cationic proteins and neurotoxins [23]. It may be premature to change the therapeutic approach based on the specific clinical subtype of CSS, as studies comparing treatment strategies for each group are lacking, and the respective global outcomes do not seem to differ significantly [47•]. Therefore, it is recommended to treat patients according to the severity of the disease.

Treatment

CSS generally has been considered a milder type of systemic vasculitis, with lower mortality compared with other types of vasculitis, and a remission rate similar to that of GPA and higher than that of MPA [48]. However, if untreated, the mortality of CSS was similar to that of untreated GPA, approaching 50% at 3 months [5•, 37].

Recent studies showed that if there were no poor prognosis factors—that is, a Five Factor Score (FFS) of 0—remission was easily induced by corticosteroids alone; however, 80% of patients still required corticosteroids for control of asthma and sinusitis after 5 years [49].

Traditionally, corticosteroids are started orally at a dose of 1 mg/kg of prednisone or equivalent, with intravenous pulses reserved for patients with more severe manifestations. In patients with poor prognosis factors (FFS ≥1), the accepted standard of care is to add oral or pulse intravenous cyclophosphamide (CYC) to the corticosteroids for 6 to 12 months, and then, after remission is achieved, to replace it with a maintenance agent such as methotrexate, azathioprine, or mycophenolate mofetil to maintain remission and decrease the dose of corticosteroids [7].

In patients with rapidly progressive disease who are not responsive to steroids or CYC, plasma exchange and intravenous gammaglobulin therapy have been used, based on small trials, but without the data support of large, placebo-controlled studies [5•]. A few case reports have shown benefit from interferon-α therapy in refractory cases [50].

Other alternatives to CYC have been explored for the treatment of ANCA-associated vasculitis given the potential side effects of this agent; the B-cell antagonist monoclonal antibody rituximab seems to be a promising alternative. The RAVE (Rituximab in ANCA-associated Vasculitis) study recently showed that rituximab is not inferior to CYC for induction of remission in patients with ANCA-associated vasculitis and has a favorable side effect profile, but the patients mainly fulfilled criteria for GPA or MPA, not specifically for CSS [51••]. In theory, this agent could be a therapeutic option for ANCA-positive CSS patients who do not respond to or have significant side effects from CYC.

Mepolizumab, a humanized monoclonal antibody against IL-5, has been used for patients with asthma and eosinophilia. A recent small study of seven patients with steroid-dependent CSS treated with mepolizumab showed that this agent was safe and well-tolerated; it significantly lowered eosinophil counts and enabled patients to significantly decrease the dose of corticosteroids. All patients experienced relapses after the mepolizumab was discontinued [52].

Conclusions

CSS is a distinct syndrome that shares many features with other forms of ANCA-associated vasculitis. Although eosinophils and ANCA have been considered the main pathogenic factors, a significant amount of new data has become available on the immunobiology of this disease, showing that Th2 cells may also play an important role in the pathogenesis of CSS. Based on clinical studies, some authors have suggested that this entity may have two clinical subtypes related to the presence or absence of ANCA—the first subtype presenting with glomerulonephritis and small vessel vasculitic features in ANCA-positive patients, and the second presenting with peripheral eosinophilia, cardiomyopathy, and eosinophil-induced tissue damage in ANCA-negative individuals.

The treatment of patients with CSS must be tailored to individual patients according to the severity of disease and the presence of poor prognostic factors (FFS); high-dose corticosteroids and cyclophosphamide are still the gold standard combination for the treatment of severe cases, but use of biological agents such as rituximab or mepolizumab seems to be a promising therapeutic alternative for patients with ANCA-associated vasculitis, including CSS.

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